

**REMARKS**

**Status of the Claims**

Claims 4-11 are pending and under examination in this application. Claims 1-3 were previously cancelled without prejudice. Claim 12 has been added, with support found throughout the specification and in particular in original claims 8-11. Upon entry of the present amendment, claims 4-12 will be pending and at issue. No new matter has been added.

**Formalities**

The Examiner has acknowledged the priority documents for this case and concluded that the priority date for the application is July 8, 2002, the filing date of the Japanese Application 2002-198941. The first paragraph of the specification has been amended to reference the complete related application information.

**Maintained and New Rejections Under 35 U.S.C. §103 (Obviousness)**

The rejection of claims 4, 5-8, and 11 under 35 U.S.C. § 103 as allegedly being obvious over Morin et al. (WO 00/46355) (“Morin”) in view of Li, et al., *Cancer Res.*, 61(17)6428-6436 (2001) (“Li”) has been maintained. Additionally, the Examiner has rejected claims 4, 5, and 8-10 as allegedly being obvious over Morin in view of Li and Cheng *et al.* (Cheng et al., U.S. Patent Application No. 2003/0104625 (“Cheng”).

The Examiner acknowledges that Morin fails to teach an adenovirus with IRES inserted between E1A and E1B, operably linked to the hTERT promoter as recited in claim 4. The Examiner relies on Morin for general teachings relating to the hTERT promoter. The Examiner relies on Li for teaching an adenoviral construct comprising a promoter AFP TRE element operably linked to an E1A-IRES-E1B cassette to cause replication and destruction of hepatocarcinoma cells.

The Examiner concludes that it would have been obvious to combine the teachings of Morin (general hTERT promoter) with the teachings of Li (promoter AFP/TRE +E1A-IRES-E1B cassette targeted to hepatocarcinoma cells) to arrive at the claimed vector and methods for killing cancer cells.

These rejections are respectfully traversed.

In order to make a showing of obviousness, the Examiner must make the four factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17-18 (U.S. 1966): (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations, such as long felt need, commercial success, and unexpected results. See *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1734, 167 L.Ed.2d 705, 715 (2007).

**The Scope and Content of the Prior Art and the Differences between the Prior Art and the Claims**

Applicants have shown in their previous responses and maintain that the differences between the cited prior art and the claims are too great to render the claims obvious. All of the pending claims require a polynucleotide cassette comprising an hTERT promoter operably linked with an E1A gene, an IRES sequence, and an E1B gene in this order, wherein the cassette is capable of replicating in a cancer cell. None of the prior art teaches or suggests these critical claim limitations, and actually teaches away from, or questions the success of, such a putative combination as described below. In particular, none of the cited references disclose or suggest the hTERT promoter for driving expression of E1A-IRES-E1B construct as recited in claim 4 and from which claims 5-12 depend. Nor would one of skill in the art be motivated to modify the separately disclosed elements in these references because there would have been no indication that such a combination would be capable of replicating in a cancer cell or function to kill cancer cells as claimed.

In contrast to the Examiner's characterization, it was not obvious to combine the teachings of Li and Morin to arrive at the claimed vectors and methods for broadly killing cancer cells. Nothing in Li or Morin teach that an hTERT promoter+ E1A-IRES-E1B construct would be able to broadly replicate in cancer cells. Neither Morin nor Li teach or suggest, or provide any expectation of success for combining an hTERT promoter with an E1A-IRES-E1B construct in the manner claimed that would broadly kill cancer cells of various types of tissues. While Morin teaches that the hTERT promoter is sufficient to drive TK gene expression (a suicide gene) *in situ* (See page 35, Example 3 in Morin), Morin does not teach or suggest, or provide any indication for the success for the combination of hTERT with any other construct, much less the E1A-IRES-E1B construct to broadly replicate in cancer cells. Furthermore, nothing in Morin provides a basis for predicting that a recombinant virus containing such a construct would kill cancer cells of various tissues by replication of the virus.

Moreover, Morin described results where only the E1A replication gene was placed under control of the hTERT promoter (See, e.g., page 41, lines 3-4; and Fig. 5). Morin is silent regarding the "E1B gene" and the combination of "E1A gene and E1B gene" under the control of the hTERT promoter. Furthermore, Morin teaches that "the genetic element essential for replication is an adenovirus E1A region." (See pg. 45). Thus, Morin provides no relevant teaching on whether the E1B gene would be driven by the hTERT promoter, and if anything suggests that the hTERT promoter would be ineffective to regulate the E1A-E1B construct separated by an IRES sequence as described by Li. In this manner, Morin leads away from insertion of IRES between E1A and E1B and is illustrative that one skilled in the art would not have been motivated to combine the hTERT promoter as described by Morin, with the E1A-IRES-E1B construct described by Li to arrive at the presently claimed invention.

Nothing in Li cures the deficiencies of Morin. Specifically, the HCC-specific oncolytic adenoviruses taught by Li replicate *only in hepatic cancer cells*. The combination of the general teachings of Morin relating to hTERT promoters and Li, hepatic cancer cell targeted constructs do not indicate any combination that would result in a polynucleotide or viral construct capable of

replicating in cancer cells, and further that replication of such recombinant viruses would kill cancer cells.

With respect to claims 4, 5, 8-10, the Examiner relies on Cheng for certain results using adenoviral constructs in brain and other tissues, including bone marrow. Nothing in Cheng hints at combining the hTERT promoter with the E1A-IRES-E1B construct, or contemplates a recombinant adenovirus containing such a construct that is capable of replicating in cancer cells including those listed in claims 9-10. Cheng describes the use of E2F-1 promoter to selectively regulate E1A expression. Cheng describes a TERT promoter operably linked to the adenovirus E4 region. Additionally, Cheng states that the E1A, E1B, and E4 coding sequences are preferred genes for viral replication. Cheng is silent regarding whether any additional genes, or gene segments can be inserted between the replication genes in such a construct, or the effects of such a construct on the ability of a recombinant virus to replicate in cancer cells or to kill cancer cells. The Examiner is attempting to combine certain general adenoviral teachings without any indication from the cited references of the success of such constructs, to arrive at the claimed invention.

In contrast to the Examiner's conclusion relating to the combination of Li, Morin, and further in combination with Cheng, a skilled artisan would have understood that the expression of E1B gene under the control of IRES sequence would not be at a sufficient level to cause tumor cell lysis via viral replication. Thus, even if a skilled artisan reading Morin decided to control the expression of E1B at the translational level, there would have been no reasonable expectation that the arrangement of IRES sequence upstream of E1B gene would successfully control the expression of E1B gene at a level sufficient to cause tumor cell lysis by viral replication. Therefore, there would have also been no expectation of success or motivation to combine any of these elements described Li, Morin, or Cheng as alleged by the Examiner.

Applicants have gone beyond any teaching or suggestion in the prior art and have found that the hTERT+ E1A-IRES-E1B construct is capable of replicating in cancer cells and killing them, thus effecting a specific and potent cancer treatment that has been long sought after by many skilled in this art.

The broad replication ability of the claimed vectors and broad ability to kill cancer cells as claimed are unexpected and extremely advantageous results that would not have been predicted by one of ordinary skill in the art at the time of the invention. Indeed, finding agents that are capable of replicating in a variety of cancer tissues is a rare and unpredictable event. Examples 1-5 illustrate such an effect of the claimed vectors and viral constructs. The nude mouse model results showing reduced tumor size of various types of tumors are illustrative of the *in vivo* effects of the claimed constructs and methods.

Furthermore, the surprising and advantageous effects of the claimed invention (including the broad ability to replicate in cancer cells, and the broad ability to kill cancer cells) are further demonstrated in initial clinical trial results, described herein in a declaration submitted under 37 C.F.R. §1.132 by one of the co-inventors of the application Dr. Toshiyoshi Fujiwara. Additionally submitted in support of the declaration is a copy Dr. Fujiwara's Curriculum Vitae (Exhibit 1), a copy of the Investigational New Drug Application (IND) (Exhibit 2); and a copy of a press release for strategic alliance and license agreement between Oncolys BioPharma and Medigen Biotechnology in support of commercial success of the claimed invention (Exhibit 3).

The clinical results described in the Fujiwara declaration demonstrate that OBP-301 (a recombinant viral construct that comprises the hTERT promoter+ E1A-IRES-E1B construct as recited in claim 4) replicates in cancer cells and kills cancer cells in various tissues when administered to a human patient (See Fujiwara Declaration at Table 2 showing tumor shrinkage after 28 days). These results also demonstrate the advantageous broad targeting ability of the claimed cassette in an adenoviral construct utilized according to the presently claimed methods for killing cancer cells. Thus, the claimed cassette and viral constructs are broadly capable of replicating in and killing cancer cells in human patients and can be used in the treatment of numerous cancer types. The cited references do not teach or suggest such constructs, recombinant viruses, or methods with the claimed features, or successful use thereof in a clinical setting.

The clinical trial described in the accompanying declaration is the first of its kind in the world demonstrating an oncolytic adenovirus replicating selectively in tumor cells of many types.

Such improvements and advantages of the claimed cassettes, adenoviral constructs, and methods are the types of results that obviate obviousness rejections consistent with the recent Supreme Court decision *KSR v. Teleflex*, 550 U.S. \_\_\_\_ (2007)<sup>1</sup> where in contrast to the presently claimed constructs and methods, the court discussed *predictable* outcomes that support a finding of obviousness stating:

The combination of familiar elements according to known methods is *likely to be obvious when it does no more than yield predictable results.*" (emphasis added) (discussing *United States v. Adams*, 383 U.S. 39, 40 (1966) (the companion case to *Graham*), *Anderson's Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969), and *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976)).

Assembling the claimed vector constructs and performing the methods in the manner discovered by the present inventors were not mere combinations that yielded predictable results. Achieving such broad targeting and killing of cancer cells using the inventive cassette, viral constructs, and the success of the claimed vectors and methods in human patients would not have been predicted by one of ordinary skill, absent the teachings of the present inventors.

Furthermore, the claimed cassettes and methods result in killing cancer cells in various tissues while also exhibiting minimal or undetectable side effects when administered to a mammal (See paragraph 0075 of US Patent Publication No.: US2006/0239967, and further Table 1 of the Fujiwara Declaration).

### **Secondary Considerations**

The Supreme Court also stated in *KSR*, that the *Graham* standard "set forth a broad inquiry and invited courts, where appropriate, to look at any secondary considerations that would prove instructive in the analysis of obviousness. (*KSR*, 127 S. Ct. at 1739). Evidence of a number of different objective factors: commercial success, long felt but unsolved need, failure of others,

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<sup>1</sup> Holding that *Graham v. John Deere* controls the obviousness inquiry and warning that a rigid application of the teaching / suggestion / motivation test as a litmus test for obviousness is inconsistent with the *Graham* framework.

copying, respect by the industry, acclaim, and unexpected results, have recently been used successfully to “overwhelmingly demonstrate[d] the nonobviousness” of the patented drug, as in the case for risperidone (Risperdal). (*Janssen*, 456 F. Supp. 2d at 673). For objective indicia to be given “substantial weight” in the obviousness inquiry, “[a] nexus between the merits of the claimed invention and the evidence of secondary considerations is required.” (See, e.g., Ortho-McNeil, 348 F. Supp. 2d. at 756).

Applicants submit herewith evidence of commercial success of the claimed invention as encompassed by the commercial product Telomelysin® (OBP-301), which is fully supported by the March 6, 2008 Press Release by assignee Oncolys BioPharma, Inc. announcing a strategic alliance and license agreement with Medigen Biotechnology Corp. (Exhibit 3). The press release describes the “total financial terms for this agreement, including up-front and milestones, may reach a total of U.S. \$198.9 million...” The license is directed to further developing and commercializing embodiments of the present invention, including Telomelysin® (OBP-301) as new tumor treatments. The licensee Medigen Biotechnology has recognized the value of the claimed invention by virtue of the substantial licensing investment and value based on Telomelysin®.

Telomelysin® (OBP-301), as described above contains the polynucleotide construct of claim 4 and is a viral construct encompassed by claim 5. The use of Telomelysin® in cancer treatments as described in the ongoing clinical trials is also encompassed by all of the pending method claims. The high value of the license agreement, *i.e.*, commercial success, of Telomelysin® is due to the ability of a recombinant virus containing the polynucleotide construct hTERT promoter+ E1A-IRES-E1B to replicate in cancer cells and kill cancer cells in various tissues when administered to a human patient. The attributes of Telomelysin® are an element of every claim at issue.

Thus, Applicants respectfully submit that evidence of commercial success has been provided and should be considered by the Examiner. The high price of the licensing deal between Oncolys BioPharma, Inc. and Medigen Biotechnology Corp. for Telomelysin® (OBP-301) and further development and commercialization aspects based on hTERT promoter+ E1A-IRES-E1B

constructs which encompass claims 4-12 of the instant application show the commercial success of the claimed invention, showing the non-obviousness of the claimed constructs and methods.

**Failure of Others and Long Felt Unsolved Need**

Finally, Applicants respectfully submit that the failure of others to find a specific and potent cancer treatment, is another secondary consideration in support of the non obviousness of the pending claims. Submitted herewith are two publications (Rodriguez *et al.*, Cancer Res., 57:2559-2563, 1997; and Kurihara *et al.*, J. Clin. Investig., 106:763-771, 2000) that describe the targeting and other problems associated with adenoviral constructs. Rodriguez *et al.* describes adenoviral constructs selective for antigen-positive prostate cancer cells. Kurihara *et al.* describes adenoviral constructs selective for human breast carcinoma cells expressing the MUC1 antigen. While these constructs target specific cancers, they do not exhibit the broad selective targeting for other types of tumors as demonstrated by the results using the claimed constructs.

The high value placed on the claimed invention as illustrated by the licensing deal described herein, is further evidence of the long felt need to find a broad and selective cancer treatment and further illustrates the advantages of the presently claimed invention. For all these reasons, it is submitted that claims 4-12 would not have been obvious and Applicants respectfully submit that the obviousness rejections should be withdrawn.

**CONCLUSION**

In view of the foregoing amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

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